

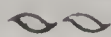
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# ECHITAMINE IN ALSTONIA BARKS

BY

J. A. GOODSON

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THE WELLCOME CHEMICAL RESEARCH LABORATORIES  
(The Wellcome Foundation Ltd.)

T. A. HENRY, D.Sc. (Lond.), *Director*

183-193, Euston Road

LONDON, N.W. 1



### 391. *Echitamine in Alstonia Barks.*

By JOHN A. GOODSON.

BARKS of various species of *Alstonia* have been examined in the hope of finding a source of echitamine richer in that alkaloid than is the bark of *A. congensis*, with a view to determine its constitution. Although the desired end has not been attained, it is thought worth while to record the figures obtained and to present further data on the alkaloids and lactones of the barks of *A. congensis*, *A. scholaris*, and *A. angustiloba*. Unfortunately, a specimen of the bark of *A. spectabilis*, R.Br., which Hesse (*Annalen*, 1880, **203**, 170) states contains 0.808% of echitamine, an amount far in excess of that in any other species examined, was not available.

A new crystalline alkaloid,  $C_{20}H_{26}O_3N_2$ , which it is proposed to call *echitamidine*, has been obtained in small quantities from the mother-liquors from echitamine hydrochloride from the barks of *A. congensis* and *A. scholaris*, and crystalline salts prepared. Two crystalline lactones of the formula  $C_9H_{14}O_3$ , one (called "lactone C") identical with that isolated from the bark of *A. congensis* (J., 1925, **127**, 1647) and which also occurs in the bark of *A. angustiloba*, have been isolated from the bark of *A. scholaris*. The second lactone is called "lactone S."

The view that echitamine is a methyl ester, which is hydrolysed



with great ease (*ibid.*, p. 1646), has been confirmed, and a ready means of preparing demethylechitamine found by boiling a solution of echitamine to which an equivalent of sodium hydroxide has been added : the methyl alcohol produced in the hydrolysis was identified as *p*-nitrobenzoate. The instability of echitamine base in aqueous solution is in marked contrast to the stability of echitamine salts, which suffer very little change when their solutions are boiled, and explains the production of demethylechitamine in attempts to crystallise echitamine base from solutions containing water.

Demethylechitamine has been reconverted into echitamine hydriodide by boiling it with methyl iodide, and into *echitamine methyl sulphate* by the action of methyl sulphate in the cold.

When an equivalent of sodium methoxide in methyl alcohol was added to echitamine hydrochloride in an attempt to prepare crystalline echitamine base, the acicular crystals of echitamine hydrochloride gave place to rhombic prisms consisting of a *compound* of the hydrochloride and methyl alcohol. It was subsequently found that the presence of sodium methoxide was not necessary for the formation of this substance. Ethyl alcohol does not form a similar compound.

Several of these barks have not been examined previously, and with the exception of *A. scholaris*, none of them is readily accessible. The author is therefore greatly indebted to the Authorities of the Imperial Institute; The Director of the Royal Botanic Gardens, Kew; Mr. A. R. Penfold, Curator of the Technological Museum, Sydney; Mr. C. F. White, Government Botanist, Brisbane, Queensland; and Dr. A. F. Fischer, Director of Forestry, Manila, Philippine Islands, for their kindness in providing the samples used in this investigation.

#### EXPERIMENTAL.

All m. p.'s recorded are corrected.

The alkaloids were prepared from the barks as described previously (*ibid.*, p. 1643). The yield of echitamine hydrochloride from different samples of bark of the same species varied considerably.

Species.	Source.	Total alkaloids, %.	Echitamine hydrochloride, %.
<i>A. angustiloba</i> , Miq.	Malaya	0.17	0.04
<i>A. congestis</i> , Engl.	Gold Coast	0.38—0.56	0.18—0.34
" "	Nigeria	0.11—0.12	0.03—0.04
" "	Cameroons	0.18	0.09
<i>A. constricta</i> , F. Muell	Australia	0.40	nil
<i>A. Gilletii</i> , De Wild	Belgian Congo	—	0.21
<i>A. macrophylla</i> , Wall	Philippines	0.99	nil
<i>A. scholaris</i> , R. Br.	Belgian Congo	—	0.04
" "	India	0.16—0.27	0.08—0.10
" "	Philippines	0.28—0.40	0.20—0.31
<i>A. spathulata</i> , Blume	Malaya	0.06	0.03
<i>A. villosa</i> , Blume	Australia	1.61	nil

Hesse (*loc. cit.*) found 0.13% of echitamine in *A. scholaris* bark, and Bacon (*Philippine J. Sci.*, 1906, 1, 1007) obtained 0.10—0.14% of echitamine hydrochloride.

*Isolation of Echitamidine.*—The bases recovered from the mother-liquors from echitamine hydrochloride from the barks of *A. congestis* and *A. scholaris* were dissolved in dil. HCl, the solution separated from tar and further purified by extraction with Et<sub>2</sub>O. To the purified solution, NH<sub>3</sub> aq. was added and the liberated bases extracted by Et<sub>2</sub>O. The bases were dissolved in a little EtOH and a warm 5% solution of picric acid in EtOH was added. Sticky ppts. were thrown down which on boiling with EtOH became cryst., tar being dissolved and removed by decantation. The crude picrate melted at 219° (decomp.). The bark of *A. congestis* gave 0.0045% of crude picrate and that of *A. scholaris* 0.0018%. The *picrate*, twice recryst. from acetone, had m. p. 226—227° (decomp.) (Found: C, 54.4; H, 5.0; N, 12.8. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 54.6; H, 5.1; N, 12.3%). The *base* was isolated by decomp. of the picrate by shaking with 20 vols. of 20% HCl, removing the picric acid by shaking with Et<sub>2</sub>O, and extraction of the aq. solution with Et<sub>2</sub>O after the addition of excess of NH<sub>3</sub> aq. It crystallises from moist Et<sub>2</sub>O in rosettes of six-sided plates, which soften at 122°, melt at 135°, and have  $[\alpha]_D^{16} - 515^\circ$  ( $c = 5$  in EtOH); m. p. 244° (decomp.). The base gives a pale green coloration with Hopkins and Cole's glyoxylic reagent, and with conc. HNO<sub>3</sub> a blue passing rapidly to green, slowly to brown, and finally to yellow, whereupon addition of excess of NaOH aq. produces a red coloration (Found, for air-dried base: loss at 105° in vac., 5.2. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·H<sub>2</sub>O requires H<sub>2</sub>O, 5.0%. Found, for dry base: C, 69.6; H, 7.4; N, 8.1. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub> requires C, 70.1; H, 7.7; N, 8.2%).

The alkaloid is a mono-acid base; the following salts were all crystallised from H<sub>2</sub>O. *Hydrochloride*, from conc. aq. solutions, prisms. The hydrated salt softened at 75°, frothed at 105°, and had  $[\alpha]_D^{16} - 473^\circ$  ( $c = 2.5$  in H<sub>2</sub>O); m. p. 179° (decomp.) (Found, for hydrated salt: loss at 60—105° in vac., 15.8. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HCl·4H<sub>2</sub>O requires H<sub>2</sub>O, 16.0%. Found, for dry salt: Cl, 9.3. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HCl requires Cl, 9.3%). *Hydrobromide*, long prisms softening at 105°, m. p. 114°; dry salt, m. p. 181° (decomp.),  $[\alpha]_D^{15} - 422^\circ$  ( $c = 2.5$  in H<sub>2</sub>O) (Found, for air-dried salt: loss at 100—105° in vac.: 9.3. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HBr·2H<sub>2</sub>O requires H<sub>2</sub>O, 7.8%). The sparingly sol. *hydriodide*, clusters of plates, m. p. 110° or 182° (dry, decomp.),  $[\alpha]_D^{16}$  for dry salt  $-389^\circ$  ( $c = 0.38$  in H<sub>2</sub>O) (Found, for air-dried salt: loss at 80—105° in vac., 10.2. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HI·3H<sub>2</sub>O requires H<sub>2</sub>O, 10.3%. Found, in dry salt: I, 27.0. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HI requires I, 27.0%).

The *sulphate*, rosettes of needles softening at 73°, m. p. 87°  $[\alpha]_D^{17} - 362^\circ$  ( $c = 1.112$  in H<sub>2</sub>O). Dry salt, m. p. 169° (decomp.) [Found, for air-dried salt: loss at 60—105° in vac., 19.8. (C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub>·11H<sub>2</sub>O requires H<sub>2</sub>O, 20.2%. Found, in dry salt: H<sub>2</sub>SO<sub>4</sub>, 12.7. (C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>)<sub>2</sub>·H<sub>2</sub>SO<sub>4</sub> requires H<sub>2</sub>SO<sub>4</sub>, 12.5%]. The *nitrate*, large prisms, softening at 86°, m. p. 103°,  $[\alpha]_D^{15} - 403^\circ$  ( $c = 1.108$  in H<sub>2</sub>O). Dry salt commenced to decompose at 137°, and frothed at 170° (Found, for air-dried salt: loss at 70—105° in vac.: 9.4. C<sub>20</sub>H<sub>26</sub>O<sub>3</sub>N<sub>2</sub>·HNO<sub>3</sub>·2H<sub>2</sub>O requires H<sub>2</sub>O, 8.2%).

Abnormal results were obtained for MeO and NMe. It is possible there is present only a methylimino-group and no methoxyl group (cf. Barger and Ewins, *J.*, 1918, 113, 235).♦



	Found.		Total AgI, calc.		Theory requires for	
	MeO,	NMe,	as MeO,	as NMe,	1MeO,	1NMe,
	%.	%.	%.	%.	%.	%.
Base .....	5.0	5.4	10.7	10.0	9.1	8.5
Picrate .....	4.4	1.7	6.2	5.8	5.4	5.1
Hydriodide	6.3	1.4	7.8	7.3	6.6	6.2

*Isolation of Lactones.*—Two cryst. lactones, C and S, have been isolated from the bark of *A. scholaris* by a modification of the method used in the case of *A. congestis* (J., 1925, 127, 1647). Lactone C is identical with the lactone of *A. congestis* bark; it also occurs in the bark of *A. angustiloba*. The yield of lactones from different samples of bark of the same species varies considerably:

Species.	Source.	Total cryst. lactones, %.	Lactone C, %.	Lactone S, %.
<i>A. congestis</i>	Gold Coast	0.020	0.020	nil
	"	0.011	0.011	nil
<i>A. scholaris</i>	India	0.047	0.016	0.031
"	Philippines	0.021	0.014	0.006
	"	0.019	0.013	0.006
<i>A. angustiloba</i>	Malaya	0.011	0.011	nil

The separation of the lactones of *A. scholaris* bark from one another by fractional crystn. from  $H_2O$  was tedious; the proportion of the two lactones present was therefore calc. from the wt. and optical rotation of the fractions obtained.

Lactone S crystallises from hot  $H_2O$  in colourless prisms, m. p. 80—84° (air-dried) or 107° (dry) (Found, in air-dried lactone: loss at 70—90° in vac., 10.6.  $C_9H_{14}O_3 \cdot H_2O$  requires  $H_2O$ , 9.6%. Found, in dried lactone: C, 63.4; H, 8.4; MeO, nil.  $C_9H_{14}O_3$  requires C, 63.5; H, 8.3%. Dissolved in excess of standard NaOH aq., the hydrated lactone neutralised 21.0% of NaOH. Calc.: 21.3%). It is neutral in reaction, less soluble in  $H_2O$  (1 in ca. 29 at 19°) than lactone C (1 in ca. 19 at 19°), and not so intensely bitter. It gives a red coloration with Hopkins and Cole's glyoxylic reagent; lactone C gives no colour.

The *monoacetyl* derivative crystallises from  $Ac_2O$  in needles, m. p. 86—90° (Found: C, 61.9; H, 7.5.  $C_{11}H_{16}O_4$  requires C, 62.2; H, 7.6%).

The two lactones had the following rotations ( $c = 2.5$ ):

	In $N-H_2SO_4$ .	In $H_2O$ .	In $N-NH_3$ .	In $N-NaOH$ .
Lactone C .....	+ 50.6°	+ 50.6°	+ 65.3°	+ 94.1°
Lactone S .....	+ 142.5	+ 143.3	+ 97.9	+ 60.1

Neither lactone reduces Fehling's solution. They do not absorb an appreciable amount of Br when kept for 24 hrs. in solution in  $CHCl_3$  containing sufficient Br to saturate one double bond. They would appear to contain one fully reduced ring (possibly hexahydrobenzene) with saturated side-chain, or chains.

*Demethylechitamine.*—Echitamine hydrochloride (20 g.) was dissolved in 400 c.c. of hot  $H_2O$ , 100 c.c. of approx. 0.5N-NaOH aq. were added, and the mixture boiled under reflux. After a few mins. demethylechitamine rapidly separated; the heating was then continued for 3 hrs. on a boiling water-bath. Cryst. substance (17.6 g.) having the characteristic properties of demethyl-

echitamine separated over-night. The MeOH produced by hydrolysis was recovered from the filtrate from the demethylechitamine by fractional distillation, and identified by conversion into *p*-nitrobenzoate. Demethylechitamine is almost tasteless, perhaps on account of its low solubility (*ca.* 1 in 645 of H<sub>2</sub>O at 19°, for hydrated substance). It has  $[\alpha]_D^{21} - 46.8^\circ$  ( $c = 2.5$  in 0.5N-H<sub>2</sub>SO<sub>4</sub>).

*Echitamine Hydrochloride-Methyl Alcohol Compound*.—MeOH (55 c.c.) containing 0.1284 g. of MeONa was added to echitamine hydrochloride (1 g.) and kept over-night, or the mixture boiled for  $\frac{1}{2}$  hr. and kept. Rhombic prisms (0.6 g.) were obtained, m. p. 277° (decomp.),  $[\alpha]_D^{16} - 52^\circ$  ( $c = 0.794$  in H<sub>2</sub>O) (Found: C, 60.6; H, 7.7; Cl, 7.9; MeO, 14.2; NMe, 7.6. C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>N<sub>2</sub>.HCl.MeOH requires C, 61.0; H, 7.4; Cl, 7.8; 2MeO, 13.6; NMe, 6.4%).

The presence of MeONa was found to be unnecessary; 1 g. of echitamine hydrochloride treated with 50 c.c. of MeOH rapidly dissolved, and 0.84 g. of rhombic prisms of the alcohol compound separated, m. p. 277° (decomp.) (Found Cl, 7.8; MeO, 13.5; NMe, 8.4%).

The substance is comparatively stable to heat, losing practically nothing on heating to 200° in vac.; the MeOH is lost on recrystn. from H<sub>2</sub>O. 1.08 G. of the compound were dissolved in hot H<sub>2</sub>O; on cooling, 0.64 g. of echitamine hydrochloride having  $[\alpha]_D^{16} - 58^\circ$  ( $c = 1$  in H<sub>2</sub>O) separated (Found Cl, 8.4; MeO, 7.4; NMe, 7.9. Calc. for C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>N<sub>2</sub>.HCl: Cl, 8.4; MeO, 7.4; NMe, 6.9%).

*Echitamine Hydriodide*.—Anhyd. demethylechitamine (3.7 g.) was heated under reflux with 15 c.c. of freshly distilled MeI during 16 hrs. and excess of MeI removed by distillation. The residue (4.9 g.), recryst. twice from hot H<sub>2</sub>O, gave 2.6 g. of long anhyd. prisms, m. p. 266° (decomp.), the decomp. point being unchanged on admixture with echitamine hydriodide (Found: MeO, 6.0; NMe, 6.5; I, 24.7. Calc. for C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>N<sub>2</sub>.HI: MeO, 6.1; NMe, 5.7; I, 24.8%). That the above hydriodide was that of echitamine was confirmed by conversion into the hydrochloride by heating its aq. solution with freshly pptd. AgCl. The hydrochloride obtained had the characteristic properties of echitamine hydrochloride.

*Echitamine Methyl Sulphate*.—Demethylechitamine (1 g.) was treated at room temp. with 6 c.c. of freshly distilled Me<sub>2</sub>SO<sub>4</sub>, and set aside for 8 days. The solid deposit gave, after two recrystns. from H<sub>2</sub>O, 0.7 g. of clusters of plates, m. p. 253° (decomp.) (Found S, 6.5; MeO, 12.2; NMe, 6.6. C<sub>22</sub>H<sub>28</sub>O<sub>4</sub>N<sub>2</sub>.MeHSO<sub>4</sub> requires S, 6.5; MeO, 12.5; NMe, 5.9%). The substance was proved to be a salt of echitamine by regeneration of the base and conversion into echitamine hydrochloride.

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WELLCOME RESEARCH INSTITUTION,  
LONDON, N.W.1.

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